

Epidemiology of Benign Breast Disease, with Special Attention to Histologic Types

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INTRODUCTION

Benign breast disease deserves attention because of its high prevalence, its impact on women's quality of life, and, for some histologic types, its cancerous potential. Identification of risk factors for benign breast disease could improve our understanding of its etiology and pathogenesis and help to define preventive strategies.

Benign breast disease has been extensively studied, and this wealth of literature warrants periodic reevaluation. This paper both updates and extends a previous review by Ernster (1) by summarizing accumulated information on the relation of benign breast disease to smoking, methylxanthines, and diet that was not covered in that earlier review. It does not, however, include a section on the relation between benign breast disease and breast cancer, a topic recently reviewed by Bodian (2). We have also attempted to consolidate the wide range of terms used to describe the histologic manifestations of this disease.

METHODS

We began by conducting a MEDLINE® search using the keywords "benign breast disease," "epidemiology," and "risk factors." The bibliographies of retrieved articles were then used to identify other references.

All autopsy and cohort studies that we were able to identify were used to estimate the frequency of benign breast disease.

We concentrated our review of risk factors on studies that used a histologic definition of benign breast disease. Studies that relied only on anamnestic (3–7) or clinical (8) definitions of benign breast disease, intervention trials in which there were no controls

(9–11), and studies for which incomplete information about methodology was provided (12, 13) were excluded from our analysis. The remaining studies were then grouped according to their methodological design into three categories: 1) case-control studies with hospital controls, 2) case-control studies with population controls, and 3) cohort and nested case-control series. Each risk factor was then studied separately. Included studies and their salient design characteristics are listed in table 1.

Breast morphology and development

Breast development and related terminology is presented in figure 1. Briefly, 1) the mammary gland develops in the embryo from an invagination of the superficial ectoderm which forms elementary ducts in the connective tissue; 2) before puberty, the ducts grow and divide in a dichotomous way; and 3) lobule formation occurs after menarche and increases with age up to about the age of 25 years (14, 15). Epithelial and stromal proliferation and regression occur regularly with menstruation, but complete differentiation with maximal development of lobular tissue takes place only through pregnancy and lactation. According to Hughes (16), regression occurs in a patchy pattern after pregnancy; involution of lobules and ducts starts at about the age of 35 years.

Russo and Russo (17) demonstrated that at the cellular level, development of the human breast was related not only to age but also to the reproductive history of the host. Russo et al. (18) then showed that the level of DNA synthesis reflecting cell proliferation decreased with age, but that parity had an even greater influence on its diminution because DNA synthesis in the human breast epithelium was significantly lower after the structures were differentiated by pregnancy (high in intralobular terminal ducts, decreasing in alveoli and ducts). Going et al. (19) and Meyer (20) further demonstrated that cell proliferation in breast lobular epithelium was higher during the second half of the menstrual cycle, even when artificially regulated by oral contraceptives.

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Abbreviations: CI, confidence interval; RR, relative risk.

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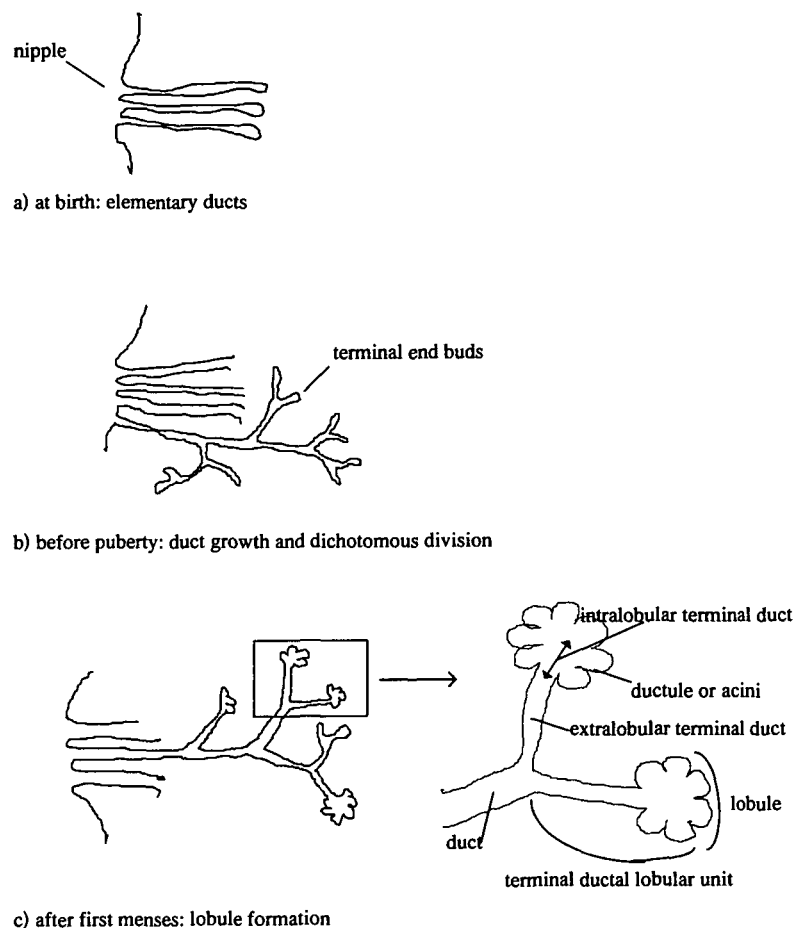


FIGURE 1. Breast development and terminology. (Adapted from Russo et al. (14) and Wellings (15).)

Definition of benign breast disease

The study of benign breast disease is difficult because of the lack of clear-cut clinical and histopathologic separation between physiologic and pathologic changes in the breast. There are numerous definitions and classifications, but two major ones dominate the epidemiologic literature, fibroadenoma and fibrocystic breast disease; more recent reports have introduced the concept of benign epithelial proliferative disorders.

Fibroadenomas are benign tumors. Macroscopically, they are pseudoencapsulated and sharply delimited; microscopically, they have both an epithelial and a stromal component. They appear to result from hyperplasia and distortion originating in a single lobule; the epithelial cells are normal, whereas connective tissue from the stromal component contains abnormal cells found only in fibroadenomas (21). *Fibrocystic breast disease*, in contrast to fibroadenoma, is an ill-defined diagnosis used by both clinicians and pathologists. Clinically, it is "a condition in which there are palpable lumps in the breast, usually associated with pain and tenderness, that fluctuates with the menstrual

cycle and that becomes progressively worse until menopause" (22, p. 1010). Fibrocystic breast disease is discussed in the literature under many names, including chronic cystic mastitis, cystic disease, cystic hyperplasia, epithelial dysplasia, and mastopathia. Histologically, lesions of fibrocystic breast disease are of epithelial origin. Microscopically, they are usually micro- and macrocysts which may (or may not) be associated with apocrine epithelium, epitheliosis, adenosis, papillomatosis, and/or solitary and multiple papillomas. These terms are clearly defined by Schnitt and Conolly (21). Briefly, *cysts* are fluid-filled structures that are round-to-ovoid in shape and that vary in size from microscopic to grossly evident. *Gross cysts*, as defined by Haagensen (23), are derived from the terminal ductal lobular unit and are large enough to produce palpable masses. The epithelium usually consists of an inner epithelial layer and an outer myoepithelial layer. Cysts can be associated with 1) *metaplasia*, in which normal epithelium evolves into *apocrine epithelium*, the type of epithelium that lines apocrine glands in the vulva, axilla, and eyelids, and is charac-

TABLE 1. Characteristics of studies of fibrocystic breast disease and fibroadenomas

Study (reference no.)	Location and year	Study design	Incident cases	Cases	Controls	Menopause	Age range (years)	Benign breast disease definition
Baghurst and Rohan* (105)	Australia, 1995	Case-control, with one hospital and one population control	Yes	First breast biopsy with epithelial proliferation in a major laboratory (n = 354)	First breast biopsy without epithelial proliferation (n = 189); matched from the electoral roll (n = 354)	All	18-75	Biopsy (reviewed), classified by degree of proliferation or atypia
BCDSP †, ‡ (121)	United States, 1973	Hospital-based case-control	Yes	Discharge diagnosis of benign breast disease (n = 98)	Acute illness or elective surgery (n = 842)	Pre-menopause	20-44	Biopsy, fibrocystic breast disease and fibroadenoma
BCDSP ‡ (96)	United States, 1974	Hospital-based case-control	Yes	Discharge diagnosis of benign breast disease in 24 hospitals (n = 52)	Acute illness or elective surgery (n = 774)	Post-menopause	45-69	Biopsy, fibrocystic breast disease and fibroadenoma
Berkowitz et al.§ (85)	United States, 1984	Hospital-based case-control	NA †	Pathology register of five hospitals (n = 633)	Surgery (n = 1,062)	All	20-74	Biopsy (reviewed), fibrocystic breast disease
Berkowitz et al.§ (86)	United States, 1984	Hospital-based case-control	NA	Pathology register of five hospitals (n = 590)	Surgery (n = 1,018)	All	20-74	Biopsy (reviewed), fibrocystic breast disease classified by degree of proliferation or atypia
Berkowitz et al.§ (70)	United States, 1985	Hospital-based case-control	NA	Pathology register of five hospitals (n = 590)	Surgery (n = 1,018)	All	20-74	Biopsy (reviewed), fibrocystic breast disease classified by degree of proliferation or atypia
Berkowitz et al.§ (64)	United States, 1985	Hospital-based case-control	NA	Pathology register of five hospitals (n = 884)	Surgery (n = 1,077)	All	20-74	Biopsy (reviewed), fibrocystic breast disease and fibroadenoma
Berkowitz et al.§ (94)	United States, 1985	Hospital-based case-control	NA	Pathology register of five hospitals (n = 143)	Surgery (n = 355)	Post-menopause	<74	Biopsy (reviewed), fibrocystic breast disease
Boyle et al.§ (66)	United States, 1984	Hospital-based case-control	NA	Pathology register of five hospitals (n = 634)	Surgery (n = 1,066)	All	20-74	Biopsy (reviewed), classified by degree of proliferation or atypia
Bright et al. (77)	United States, 1989	Hospital-based case-control	Yes	Incident cases during the year after a diagnostic mammography (n = 172)	Screening or baseline mammography (n = 134)	All	>20	Biopsy (reviewed), fibrocystic breast disease and fibroadenoma
Brinton et al. (51)	United Kingdom, 1981	Cohort nested case-control	Yes?	From the >17 000 women of the Oxford Family Planning Association Contraceptive Study (n = 686)	Matched (n = 686)	Pre-menopause	25-39 at recruitment	Pathology register, hospital records, fibrocystic breast disease and fibroadenoma
Canry et al.§ (53)	United States, 1988	Hospital-based case-control	NA	Pathology register of five hospitals (n = 251)	Surgery (n = 1,081)	All	20-74	Biopsy (reviewed), fibroadenoma
Cole et al. (47)	United States, 1978	Population-based case-control	Yes	Pathology registers of 25 hospitals (n = 678)	Resident list, group-matched for age (n = 1,807)	All	>20	Pathology register, fibrocystic breast disease and fibroadenoma
Duffy et al. (73)	Scotland, 1983	Hospital-based case-control	No	Discharge diagnosis from surgery (n = 188)	Invited in the Breast Screening Clinic, selected in general practitioner lists (n = 2,213)	All	40-54	"Surgically confirmed", fibrocystic breast disease

Emster et al. (122)	United States, 1982	Randomized trial	No	Breast Screening Clinic, with clinical benign breast disease, instructed to stop caffeine consumption (<i>n</i> = 72)	Breast Screening Clinic, with clinical benign breast disease, no instructions (<i>n</i> = 68)	All	19-66	Clinical examination, fibrocystic breast disease and fibroadenoma
Fasal and Paffenbarger (75)	United States, 1975	Hospital-based case-control	No	19 hospitals (<i>n</i> = 446)	Matched, medical wards (<i>n</i> = 433); matched, surgical wards (<i>n</i> = 439)	All	<50	Biopsy (reviewed), fibrocystic breast disease and fibroadenoma
Fleming et al. (49)	Australia, 1982	Population-based case series	NA	Pathology, hospital and cancer registers (<i>n</i> = 1,283)		All		Pathology register, fibrocystic breast disease and fibroadenoma
Franceschi et al.† (63)	Italy, 1984	Hospital-based case-control	Yes	Referred for biopsy in a second-level hospital (<i>n</i> = 288)	Acute illness except oncologic, gynecologic, or digestive trouble in three hospitals (<i>n</i> = 285)	All	17-64	Biopsy (reviewed), fibrocystic breast disease and fibroadenoma
Hislop and Elwood (52)	Canada, 1981	Cohort		Symptomatic mastopathies—107 biopsied, of 1,374 nursing students (<i>n</i> = 215)		All		Pathology register, anamnestic, fibrocystic breast disease and fibroadenoma
Hislop et al. (79)	Canada, 1990	Screening-based case-control	No	From the National Breast Screening Study (<i>n</i> = 398)	From the National Breast Screening Study (<i>n</i> = 398)	All	40-59	Biopsy (reviewed), classified by degree of proliferation or atypia
Hsieh et al. # (83)	United States, 1984	Cohort nested case-control	Yes?	(<i>n</i> = 232)	(<i>n</i> = 1,000)	All		Biopsy (reviewed), classified by degree of proliferation or atypia
Hsieh et al. # (72)	United States, 1984	Cohort nested case-control	Yes	(<i>n</i> = 218)	(<i>n</i> = 928)	All		Biopsy (reviewed), classified by degree of proliferation or atypia
Ingram et al.** (103)	Australia, 1991	Population-based case-control	No	Pathology reports (<i>n</i> = 186)	Matched, electrolar rolls (<i>n</i> = 209)	All	19-72	Biopsy (reviewed), classified by degree of proliferation or atypia
Ingram et al.** (78)	Australia, 1989	Population-based case-control	NA	Pathology reports (<i>n</i> = 192)	Electrolar rolls (<i>n</i> = 211)	All	19-72	Biopsy (reviewed) classified by degree of proliferation or atypia
Jick et al. (50)	United States, 1988	Cohort	NA	From the "Group Health Cooperative" (<i>n</i> = 142)		Post-menopause	50-64	Pathology register, fibrocystic breast disease
Kelsey et al.†† (57)	United States, 1974	Hospital-based case-control	Yes	(<i>n</i> = 384)	Matched, surgery (<i>n</i> = 384)	Pre-menopause	20-44	Pathology register, fibrocystic breast disease and fibroadenoma
Kelsey et al.†† (62)	United States, 1978	Hospital-based case-control	NA	(<i>n</i> = 366)	Matched, surgery (<i>n</i> = 366)	Pre-menopause	20-44	Biopsy (reviewed), fibrocystic breast disease and fibroadenoma
La Vecchia et al.† (67)	Italy, 1985	Hospital-based case-control	Yes	Referred for biopsy in a second-level hospital (Milan Tumor Institute) (<i>n</i> = 288)	Acute illness except oncologic, gynecologic, or digestive in three hospitals (<i>n</i> = 285); screening for cervical cancer at Milan Tumor Institute (<i>n</i> = 291)	All	17-64	Pathology register, fibrocystic breast disease and fibroadenoma
Lawson et al.‡ (123)	United States, 1981	Hospital-based case-control	Yes	Discharge diagnosis (<i>n</i> = 210)	Matched 3:1 acute illness or surgery (<i>n</i> = 630)	All		Hospital records, fibrocystic breast disease

Table 1 continues

TABLE 1. Continued

Study (reference no.)	Location and year	Study design	Incident cases	Cases	Controls	Menopause	Age range (years)	Benign breast disease definition
Lees et al. (82)	Canada, 1978	Hospital-based case-control	No	Referred in a diagnostic breast clinic, biopsied (<i>n</i> = 692)	Matched 3:1 acute illness or surgery (<i>n</i> = 630)	All		Hospital records, fibrocystic breast disease
Lees et al. (82)	Canada, 1978	Hospital-based case-control	No	Referred in a diagnostic breast clinic, biopsied (<i>n</i> = 692)	Referred in a diagnostic breast clinic, not biopsied (<i>n</i> = 548)	All		Pathology register, fibrocystic breast disease and fibroadenoma
LiVolsi et al. †† (84)	United States, 1978	Hospital-based case-control	NA	(<i>n</i> = 205)	Matched, surgery (<i>n</i> = 205)	Pre-menopause	20-44	Biopsy (reviewed), classified by degree of proliferation or atypia
London et al. (71)	United States, 1992	Hospital-based case-control	NA	Evaluated for breast problems, biopsy of proliferative disease (<i>n</i> = 173)	Evaluated for breast problem, with biopsy of non-proliferative disease or no biopsy (<i>n</i> = 403)	Post-menopause	55-68	Pathology register, classified by degree of proliferation or atypia
Lubin et al. †† (111)	Israel, 1985	Case-control with one hospital and one population control	No	Surgery and pathology records (<i>n</i> = 854)	Surgery (<i>n</i> = 755); neighborhood (electoral rolls) (<i>n</i> = 723)	All		Biopsy (reviewed), classified by degree of proliferation or atypia
Lubin et al. †† (102)	Israel, 1989	Case-control with one hospital and one population control	No	Surgery and pathology records (<i>n</i> = 854)	Surgery (<i>n</i> = 755); neighborhood (electoral rolls) (<i>n</i> = 723)	All		Biopsy (reviewed), classified by degree of proliferation or atypia
Marshall et al. (124)	United States, 1982	Hospital-based case-control	NA	Hospital discharge diagnosis (<i>n</i> = 323)	Non-neoplastic diseases except breast (<i>n</i> = 1,458)	All	≥20	Hospital records, fibrocystic breast disease
Nomura et al. (56, 125)	United States, 1976, 1977	Population-based case-control	No	Pathology register (<i>n</i> = 320)	Matched, from the census list (<i>n</i> = 320)	All	20-49	Pathology register, fibrocystic breast disease and fibroadenoma
Ory et al. (46)	United States, 1976	Cohort	Yes	From 67,500 (<i>n</i> = 582)		All		Pathology register, fibrocystic breast disease and fibroadenoma
Parazzini et al. † (60)	Italy, 1984	Hospital-based case-control	Yes	Referred for biopsy in a second-level hospital (<i>n</i> = 288)	Acute illness except oncologic, gynecologic, or digestive trouble in three hospitals (<i>n</i> = 285)	All	17-64	Pathology register, fibrocystic breast disease and fibroadenoma
Parazzini et al. † (65)	Italy, 1991	Hospital-based case-control	Yes	Referred for biopsy in a second-level hospital (<i>n</i> = 288)	Screening for cervical cancer at the Milan Tumor Institute, (<i>n</i> = 291)	All	17-64	Pathology register, fibrocystic breast disease and fibroadenoma
Pastides et al. §§ (81)	United States, 1983	Hospital-based case-control	NA	(<i>n</i> = 125)	Matched, surgery, orthopedics, and ear, nose, and throat (<i>n</i> = 129)	All	20-44	Biopsy (reviewed), classified by degree of proliferation or atypia
Pastides et al. §§ (69)	United States, 1985	Hospital-based case-control	No	(<i>n</i> = 255)	Surgery, orthopedics, and ear, nose, and throat (<i>n</i> = 790)	All	20-74	Biopsy (reviewed), classified by degree of proliferation or atypia
Pastides et al. §§ (95)	United States, 1987	Hospital-based case-control	NA	(<i>n</i> = 255)	Surgery, orthopedics, and ear, nose, and throat (<i>n</i> = 787)	All	20-74	Biopsy (reviewed), classified by degree of proliferation or atypia

Ravnihar et al. (61)	Yugoslavia, 1979	Hospital-based case-control	Yes	(n = 497)	Matched, dermatology ophthalmology, surgery (n = 497)	All	15-64	Biopsy (reviewed), fibrocystic breast disease and fibroadenoma
Rohan et al.* (76, 98, 101, 112)	Australia, 1989, 1990	Case-control with one hospital and one population control	Yes	First breast biopsy with epithelial proliferation in a major laboratory (n = 383)	First breast biopsy without epithelial proliferation (n = 192); matched from the electoral roll (n = 383)	All	18-75	Biopsy (reviewed), classified by degree of proliferation or atypia
Sartwell et al. (58)	United States, 1973	Hospital-based case-control	Yes	(n = 416)	Matched, all wards except gynecology and urology (n = 416)	All	20-70	Pathology register, fibrocystic breast disease and fibroadenoma
Sartwell et al. (59)	United States, 1978	Hospital-based case-control	NA	(n = 938)	Matched, all wards except gynecology and psychiatry (n = 938)	All	20-69	Pathology register, fibrocystic breast disease and fibroadenoma
Schaller et al. (68)	United States, 1986	Screening-based case-control	NA	From >280,000 women in BCDDP (n = 1,569)	Not referred for surgery (n = 1,846)	All		Biopsy (reviewed), classified by degree of proliferation or atypia
Simard et al.††† (8)	Canada, 1993	Screening-based case-control	No	From 6,232 women in the National Breast Screening Study (n = 334)	Matched for age (n = 340)	All	40-59 at entry	Clinical examination, fibrocystic breast disease
Simard et al.††† (74)	Canada, 1990	Screening-based case-control	NA	From 9,089 women in the National Breast Screening Study (n = 340)	Matched for age (n = 343)	All	40-59 at entry	Pathology register plus hospital records, fibrocystic breast disease
Soini et al. (48)	Finland, 1981	Population-based case-control	NA	Pathology registers (n = 422)	Matched for age, population registry (n = 422)	All		Biopsy (reviewed), classified by degree of proliferation or atypia
Trapido et al. (55)	United States, 1984	Screening-based case-control	NA	From >280,000 women in BCDDP (n = 929)	Not referred for evaluation or biopsy (n = 846)	Post-menopause		Pathology register, fibrocystic breast disease and fibroadenoma
Vessey et al. (80)	United States, 1971	Hospital-based case-control	NA	(n = 166)	Medicine or surgery (n = 166)	Pre-menopause	16-39	Biopsy (reviewed), fibrocystic breast disease and fibroadenoma
Vobecky et al.††† (104)	Canada, 1993	Screening-based case-control	No	From 9,089 women in the National Breast Screening Study (n = 334)	Matched for age (n = 340)	All	40-59 at entry	Pathology register plus clinical examination, fibrocystic breast disease
Yu et al.* (54)	Australia, 1992	Case-control with one hospital and one population control	Yes	First breast biopsy with fibroadenoma in a major laboratory (n = 117)	First breast biopsy without epithelial proliferation (n = 192); matched from the electoral roll (n = 117)	All	18-75	Biopsy (reviewed), fibroadenoma

* The following references use data from the same study (54, 76, 98, 101, 105, 112).

† Abbreviations: BCDDP, Boston Collaborative Drug Surveillance Program; NA, not applicable.

‡ The following references use data from the same study (96, 121, 123).

§ The following references use data from the same study (53, 64, 66, 70, 85, 86, 94).

¶ The following references use data from the same study (60, 63, 65, 67).

The following references use data from the same study (72, 83).

** The following references use data from the same study (78, 103).

†† The following references use data from the same study (57, 62, 84).

‡‡ The following references use data from the same study (102, 111).

§§ The following references use data from the same study (69, 81, 95).

¶¶ The following references use data from the same study (8, 74, 104).

terized by granular eosinophilic cytoplasm and apical cytoplasmic protrusions, or 2) *hyperplasia*, which can produce *epitheliosis* and *adenosis*. In *epitheliosis* (also termed ductal or lobular hyperplasia), one cell type proliferates within the existing ductal or lobular structure. Adenosis is the development of new lobular or ductal structures, with proliferation of epithelial and myoepithelial cells. In sclerosing adenosis, the myoepithelial component predominates. The term *papillomatosis* is confusing because it is used both for *epitheliosis* (by Foote and Stewart (24) and by Haagensen (23)) and for multiple microscopic or macroscopic ductal papillomas, distinguished by vascular stalks.

The concept of *benign epithelial proliferative disease* identifies the histologic characteristics of benign breast disease that have a cancerous potential. The term includes hyperplasias and neoplasias involving the various segments of the ductal and lobular system, and which mostly arise from the terminal ductal lobular unit where the proliferation rate is maximal. Grading systems based on the degree of atypia and/or hyperplasia have been developed by Wellings et al. (15), Black and Chabon (25), Page et al. (26), and Azzopardi (27) with which to examine the precancerous potential of different histologic subcategories; these grading systems have been reviewed by Cook and Rohan (28). Finally, a classification system based on the work of Page and Dupond (26, 29, 30) was adopted at the 1985 consensus meeting of the College of American Pathologists (31), wherein fibrocystic breast disease lesions were divided into three groups according to the subsequent risk of breast cancer: nonproliferative lesions, proliferative lesions without atypia, and atypical hyperplasias. *Nonproliferative lesions* include cysts, papillary apocrine changes, epithelial-related calcifications, mild hyperplasias (between two and four epithelial cell layers within ducts), and fibroadenomas. *Proliferative lesions* without atypia include moderate or florid hyperplasias (more than four epithelial cell layers, with a tendency to bridge or distend the ducts), intraductal papillomas, and sclerosing adenosis. *Atypical hyperplasias* are proliferative lesions that possess some but not all of the features of carcinoma in situ; they can be divided into two groups, atypical ductal hyperplasias and atypical lobular hyperplasias. Proliferative lesions without atypia and atypical hyperplasia are termed *proliferative diseases*.

Hughes et al. (32) developed the concept of aberrations of normal development and involution as a classification framework for benign breast disease based on pathogenesis. For each period of breast development linked to reproductive life, both normal breast changes and associated possible aberrations of devel-

opment (aberrations which lead first to benign breast "disorder" and finally to benign breast "disease") are described. This classification system covers the whole spectrum of benign breast disease conditions. Accordingly, a fibroadenoma develops from a single lobule as a result of lobular hyperplasia; it is classified as a benign breast "disorder" or, if its size exceeds 5 cm, as a benign breast "disease" (giant fibroadenoma). The changes usually linked to fibrocystic disease (e.g., cysts, sclerosing adenosis, and simple hyperplasias) are aberrations of involution and are classified as benign breast "disorders." At the end of the spectrum, atypical and lobular hyperplasias are classified as benign breast "diseases."

Frequency of benign breast disease

Estimating the incidence of benign breast disease in the general population is difficult, because it is not a life-threatening condition and it does not necessarily come to medical attention. Women who are diagnosed and receive medical care are therefore a selected subset of all cases. Thus, the actual detection rate is not known and can only be approximated by comparing the prevalence rates of benign breast disease obtained from autopsy studies with the cumulative incidence rates from cohort studies.

In a review of eight autopsy series performed between 1919 and 1957 (Davis et al. (33)), the prevalence rate of fibrocystic breast disease (defined as macrocysts, microcysts, or epithelial hyperplasia) among women who, during their lifetimes, had no symptoms of benign breast disease was 58.5 percent (424 cases/725 autopsies). These early studies were consistent with the results of 12 other autopsy studies published since 1937 (13, 34–44). In two more recent series reported by Nielsen et al. (40) and Bartow et al. (43), the prevalence of cysts was 54 percent and 61 percent, respectively, in Caucasian subjects. The prevalence of fibroadenoma was reported in four studies (34, 41, 43, 44), and it varied, in the studies performed after 1980, from 15 percent (41) to 23 percent (44). It is noteworthy that the prevalence of fibroadenoma may be higher in black women than in white women (45). Thus, about one out of every two women may develop some degree of fibrocystic breast disease during her lifetime, and one out of every five women may develop fibroadenoma. These figures can be contrasted with the incidence rates computed from the cohort studies described below.

Seven cohort studies published between 1976 and 1986 examined the incidence of benign breast disease; five of these studies included only cases confirmed by biopsy (46–50), and two compared rates of biopsied and unbiopsied symptomatic disease (51, 52). The

age-specific incidence of biopsy-proven fibrocystic breast disease or fibroadenoma was relatively consistent across these studies.

Four comparable studies (46, 47, 49, 50) were pooled notwithstanding heterogeneous designs: The first study reported hospitalization rates in a cohort of 67,500 women (46); the second was a case-control study based on a population of 485,000 women (47); the third reported on an Australian population-based case series (49); and the fourth reported on hospitalization rates of fibrocystic breast disease in a cohort of menopausal members of a health cooperative (50). Age-specific incidence rates are shown in figure 2. The incidence rate per 100,000 woman-years of fibrocystic breast disease increases progressively from 137 at ages 25–29 years to 411 at ages 40–44 years and to 387 at ages 45–49 years, and then decreases regularly. The incidence of fibroadenoma peaks at 115 at ages 20–24 years, decreases regularly until the ages of 45–49 years, and remains close to 5 for women of older ages. The cumulative incidence of biopsy-proven fibrocystic breast disease before the age of 65 years in these four studies was 8.8 percent; the corresponding cumulative incidence of fibroadenoma was 2.2 percent. Thus, compared with autopsy studies, only 10–20 percent of benign breast disease cases are histologically diagnosed. Epidemiologic studies may thus be focusing on the most severe forms of disease.

FACTORS ASSOCIATED WITH BENIGN BREAST DISEASE

For the analysis of risk factors, benign breast disease was separated into two subgroups, fibrocystic breast disease and fibroadenoma. Fibroadenoma represents the smaller subgroup, even though it is the most common form of benign breast disease in women aged less than 30 years. Two studies included only fibroadenoma: Canny et al. (53) conducted a hospital-based

case-control study, and Yu et al. (54) used two types of controls, negative breast biopsy controls and population controls. The other studies that separated fibroadenoma from fibrocystic breast disease comprised one cohort study (46), one cohort-nested case-control study (51), one screening-based case-control study (55), two population-based case-control studies (47, 56), and 13 hospital-based case-control studies (49, 57–68). Studies in which the analysis of fibroadenomas was not conducted separately usually were concerned mostly with fibrocystic breast disease; these studies are listed in table 1, but their findings are not considered in our review, because mixing the two pathologic entities confuses rather than clarifies the search for their specific etiologies.

Age at menarche

Age at menarche is not associated with either fibrocystic breast disease or fibroadenoma. This association has only been assessed in case-control studies, none of which have suggested that age at menarche influences the subsequent risk of benign breast disease (46, 47, 51, 52, 54, 58, 59, 61, 69–72).

Age at menopause

Age at menopause may possibly be related to fibrocystic breast disease but not to fibroadenoma. The evidence in favor of an increased risk of fibrocystic breast disease with later age at natural menopause comes from four hospital-based studies (58–60, 70) and two population-based case-control studies (47, 73). Cole et al. (47) reported the relative risks to be 1.4 and 3.0 for ages at menopause of 49–51 and >52 years, respectively, relative to ages at menopause of <49 years (p for trend = 0.0005). Studies with more refined histologic definitions of benign breast disease (48, 69, 71) found no association.

Nulliparity

Nulliparous women may be at increased risk of fibrocystic breast disease but not of fibroadenoma. One hospital-based case-control study (57) and one cohort study (52) found an increased risk of fibrocystic breast disease for nulliparous versus parous women. In the study by Cole et al. (47), this positive association was restricted to women under 40 years of age (relative risk (RR) = 2.2, 95 percent confidence interval (CI) 1.4–3.6). Studies generally showed no association of nulliparity with fibroadenoma (56, 58, 59, 61).

Multiparity

A higher parity may be protective against fibrocystic breast disease but not against fibroadenoma. In a

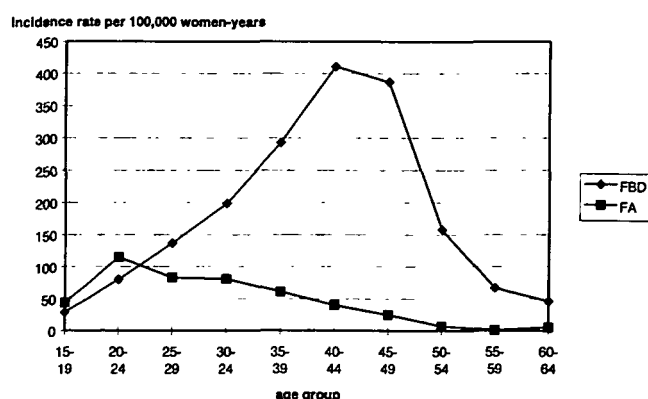


FIGURE 2. Incidence rates of fibrocystic breast disease and fibroadenoma, by age group.

nested case-control study (72), the relative risk was 0.5 (95 percent CI 0.3–0.8) for having five or more births versus one or two births. Ory et al. (46) found that the age-standardized hospitalization rates per 1,000 person-years were 5.1 for nulliparae versus 2.4 for women with parity ≥ 5 . This protective effect was, however, absent (69) or not statistically significant (71) in studies using a more refined histologic definition. The association of fibroadenoma with parity has not received much attention, and the limited available data are inconsistent: Yu et al. (54) found a protective effect for fibroadenoma using population controls but not when using biopsy controls.

Age at first live birth

Findings relating late age at first live birth to fibrocystic breast disease are inconsistent. A positive association with fibrocystic breast disease was observed only in hospital-based case-control studies (59, 60, 69). Pastides et al. (69) found a relative risk of fibrocystic breast disease of 1.7 (95 percent CI 1.2–2.4) for each 5-year increase in age at first birth among women aged <45 years, but this association was not supported by population-based case-control studies (47, 56, 73) nor by cohort studies (46, 72). Reported findings of fibroadenoma with age at first live birth have been consistently negative (46, 47, 54, 56–61).

Breastfeeding

Studies which examined the relation of ever breastfeeding with benign breast disease failed to show an association with either fibrocystic breast disease or fibroadenoma (52, 54, 56, 57, 69).

Overall, the most salient findings related to reproductive and menstrual history are that being parous, being multiparous, and being young at natural menopause may protect against fibrocystic breast disease. The risk of fibroadenoma does not appear to be influenced by reproductive factors. Age at menarche, age at first live birth (even after adjustment for the total number of live births), and breastfeeding do not seem to be related to either fibrocystic breast disease or fibroadenoma. Results by degree of atypia were not fully consistent with this conclusion, but studies were few and did not systematically include all reproductive variables.

Education

Studies in which the compared groups were not matched on a socioeconomic variable (56, 61, 69, 72, 74) showed that a higher level of education was positively related to fibrocystic breast disease. Hsieh et al. (72) found a relative risk of 1.07 (95 percent CI

1.01–1.14) for each additional 1 year of education. Nomura et al. (56) reported a relative risk of 1.8 ($p < 0.05$) for ≥ 13 years versus <11 years of education. There was, however, no difference by degree of atypia (69, 72). Education has not been shown to be a risk factor for fibroadenoma (56, 61).

Socioeconomic status

In studies that compared groups using higher socioeconomic status as a risk factor, most (47, 49, 51) but not all (56, 61) found it to be positively associated with fibrocystic breast disease. In the study by Brinton et al. (51), risks for social classes 2, 3, and 4 relative to social class 1 (highest) were, respectively, 0.71, 0.47, and 0.82 (p for trend < 0.05). In contrast to what was observed for education, fibroadenoma was associated with higher socioeconomic status in one nested case-control study (51) and in one hospital-based case-control study (57), while other studies showed no significance (56) or no association (47).

Race

In 1981, Ernster (1) noted that there was a lack of data about race/ethnicity and benign breast disease. The situation has not dramatically changed since that time. The lack of relevant data stems from the fact that many studies of benign breast disease only include white women or match controls to cases on the basis of race (e.g., Fasal and Paffenbarger (75)). No association has been found between race and degree of atypia (69) or between race and histopathologic components of fibrocystic breast disease (70).

Overall, both higher education or socioeconomic status are more consistently related to fibrocystic breast disease than to fibroadenoma. These positive associations have been attributed to selection bias, because women with benign breast disease who consult a physician and undergo breast biopsy are more likely to come from a higher socioeconomic level (see the section "Potential biases" below). However, confounding by other variables known to be associated with socioeconomic status and fibrocystic disease, such as parity and obesity, has not been ruled out. The effect of race on benign breast disease cannot be assessed with the available evidence.

Family history of breast cancer

A family history of maternal breast cancer has not been found to be related to fibrocystic breast disease, degree of atypia, or fibroadenoma in most hospital-based studies (61, 71) and population-based case-control studies (56, 73), nor in a nested case-control study (72). Pastides et al. (69), however, found a

relative risk of 2.8 (95 percent CI 1.5–5.3) for fibrocystic breast disease for a history of breast cancer in a mother or a sister of the case.

Obesity

Of all the risk factors reviewed, obesity had the strongest and most consistent association with both fibroadenoma and fibrocystic breast disease. Results of all of the studies reviewed are consistent in finding a protective effect, even though obesity was defined in a variety of ways, e.g., according to current or past body mass index (kg/m^2), highest-ever body mass index, weight, skinfold thickness, and breast size. A strong protective effect of obesity for fibroadenoma appeared in five studies (47, 48, 51, 54, 61) out of six (only the study by Parazzini et al. (60) did not show this strong protective effect). As is shown in table 2, a body mass index over the cutoff value for overweight ($25 \text{ kg}/\text{m}^2$) more than halved the risk of fibroadenoma when cases were compared with either population controls or biopsy controls (54). This same study was unique in finding that fibrocystic breast disease cases had a lower body mass index than did both types of controls (76), in contrast with nine studies of fibrocystic breast disease (47, 48, 51, 52, 69, 74, 77–79) that showed a protective effect of obesity. In a nested case-control study conducted in the United Kingdom, Brinton et al. (51) found similar relative risks for fibrocystic breast disease and body mass index as those observed by Yu et al. (54) for fibroadenoma (table 2). It is not possible to determine meaningfully whether the inverse association differs according to menopausal status, since only two studies (47, 71) separated premenopausal women from postmenopausal women. The one study comprising only postmenopausal women found no effect (71). Cole et al. (47) found a protective effect of obesity for fibrocystic breast disease and fibroadenoma that was similar in all age groups. No interaction with degree of atypia has been reported.

The possibility that the relation between obesity and benign breast disease is due to detection bias is discussed below (see "Potential biases").

Oral contraceptives

Several studies have found that oral contraceptive use has a protective effect on the risk of fibrocystic breast disease. Strong evidence is provided by the relation of fibrocystic breast disease to duration of oral contraceptive use found in many hospital-based case-control studies (46, 57, 58, 61, 62, 80, 81) and in all of the cohort studies (51, 82, 83). As is shown in table 3, the risk of fibrocystic breast disease declined with longer duration of oral contraceptive use in all of the tabulated studies. There are indications that the protective effect of duration of oral contraceptive use may be stronger in severe atypias (81, 83, 84).

Other evidence seems, however, to contradict a possible protective effect of oral contraceptive use for fibrocystic breast disease. First, trends of increased protection with longer duration of oral contraceptive use have usually been reported relative to women who have never used oral contraceptives. These trends are much weaker when computed relative to short-term oral contraceptive use, as shown in table 3. For example, Canny et al. (53) found that the trend became statistically nonsignificant when computed among oral contraceptive users only. Second, two reports from the same carefully designed case-control study with biopsy controls (85, 86) found no association between a longer duration of oral contraceptive use and risk of fibrocystic breast disease in premenopausal women.

Third, the reported association of fibrocystic breast disease with ever or current use of oral contraceptives is inconsistent. In contrast with the duration of oral contraceptive use, most studies failed to find a protective effect of ever use of oral contraceptives for fibrocystic breast disease or fibroadenoma (with the notable exceptions of two cohort-based studies (51, 83)). Current oral contraceptive use has been less extensively

TABLE 2. Association (relative risks) of body mass index and fibroadenoma or fibrocystic breast disease in two studies

Histologic type and study (reference no.)	Control type	Body mass index (kg/m ²)			
		<21	21–22	23–24	≥25
Fibroadenoma					
Yu et al. (54)	Population	1.0	1.0	0.7	0.4
Yu et al. (54)	Biopsy	1.0	0.8	0.5	0.4
Brinton et al. (51)	*	1.0	0.5	0.3	0.2
Fibrocystic breast disease					
Brinton et al. (51)	*	1.0	0.9	0.7	0.7

*Oxford Family Planning Association, nested case-control study.

TABLE 3. Association (relative risks) of oral contraceptive use and fibrocystic breast disease in three cohort and two case-control studies

Study (reference no.)	Years of oral contraceptive use													
	<1	<2	1-2	2	>2	2-5	3-4	4	5-6	≥5	6	7-8	8	≥9
Cohort														
Brinton et al. (51)		1.0		0.7				0.4			0.5		0.3	
Hsieh et al. (83)	1.0			0.6			0.6	0.6		0.4				
Ory et al. (46)	1.0			0.8	0.4									
Case-control														
Canny et al. (53)	1.0		0.7				1.2		1.2			0.6		0.6
Sartwell et al. (58)	1.0		0.7			0.3				0.2				

investigated than ever use or duration of use. No study showed an increased risk, and two studies showed a protective effect for fibrocystic breast disease or fibroadenoma (51, 63). The inconsistency between duration of use and ever or current use may mean that at least 1 year of oral contraceptive use is necessary to confer a protective effect. In ever or current users, the protective effect may thus be diluted by the prevalence of a large number of short-term users among controls.

Finally, Fechner (87) showed no differences in the histologic features of fibrocystic breast disease between 25 users and 25 nonusers of oral contraceptives. Similar negative findings were reported by others (88, 89).

The situation for fibroadenoma is quite similar to that for fibrocystic breast disease, i.e., a longer duration of oral contraceptive use appears to be protective against fibroadenoma (46, 51, 53). Kelsey et al. (62) found a strong protective effect (RR = 0.1, 95 percent CI 0.0-0.7) in women who used oral contraceptives for more than 5 years, whereas, to our knowledge, no epidemiologic study has showed a deleterious effect. Case series comparing the histologic features of fibroadenoma in oral contraceptive users and nonusers do not show clear differences (87, 90-92).

The literature on oral contraceptives use and benign breast disease does not provide a clear picture of the influence of the different types of oral contraceptives on the risk of either fibrocystic breast disease or fibroadenoma. The results of the four studies (51, 62, 85, 93) that have addressed this issue are inconsistent. Differences in effect related to the content of oral contraceptives may be responsible for the heterogene-

ity found. The changing content of successive generations of oral contraceptives could also explain discrepancies between older and more recent studies (85).

Several mechanisms have been proposed that could generate a spurious protective effect of oral contraceptives on fibrocystic breast disease or fibroadenoma. Hsieh et al. (83) have postulated that oral contraceptives may reduce the symptoms of benign breast disease and therefore hamper detection, but not affect associated cellular pathologic developments in any important way.

The possibility of surveillance bias is discussed below (see "Potential biases").

Estrogen replacement therapy

Evidence suggests that prolonged exposure to estrogen replacement therapy increases the risk of fibrocystic breast disease. An approximate twofold increased risk of fibrocystic breast disease was present for ever use of estrogen replacement therapy in cohort studies (50, 55) and in hospital-based case-control studies (86, 94, 95). Duration of estrogen replacement therapy use was consistently associated with fibrocystic breast disease in the study of Jick et al. (50) (for >5 years' use, RR = 3.7, 95 percent CI 1.6-8.4; no trend was present with longer duration of use), in the study of Trapido et al. (55), and in the hospital-based case-control studies (86, 94, 95). Berkowitz et al. (94) found a relative risk of 4.3 (95 percent CI 2.2-12.3) for >10 years of estrogen replacement therapy use in menopausal women. Important results are summarized in table 4.

TABLE 4. Association (relative risks) of estrogen replacement therapy use and fibrocystic breast disease in three studies

Study (reference no.)	Duration of estrogen replacement therapy use in years						
	≤1	<2	1-2	1-4	2-4	≥3	≥10
Nomura and Comstock (125)		1.0			0.7		3.5
Trapido et al. (55)		1.0					1.4
Pastides et al. (95)	1.0		1.6			3.6	1.4

On the other hand, some studies showed no effect for ever use (58, 60, 61) or current use (61, 94, 96) of estrogen replacement therapy on fibrocystic breast disease. Bright et al. (77) found a protective effect (odds ratio = 0.4, 95 percent CI 0.1–0.9).

The only study (86) which stratified by histologic degree of atypia found no difference in risk for ever use or ≥ 5 years' use of estrogen replacement therapy across the various degrees of atypia. Fechner et al. (97), in a histopathologic study, did not observe any significant difference in the frequency of epithelial hyperplasia or type of lesions between two groups, each of which consisted of 41 women, who had received or not received estrogen replacement therapy.

Although fibroadenoma is predominantly a premenopausal disease, its relation to estrogen replacement therapy has been studied because of concerns that this type of therapy could stop the involution of the mammary gland and increase the prevalence of fibroadenoma in postmenopausal women. The study by Canny et al. (53), in contrast to five other studies (54, 55, 58, 60, 61), found an elevated risk in women aged >45 years (RR = 3.1, 95 percent CI 1.1–9.4) for ever use of estrogen replacement therapy and for use of >1 year's duration (RR = 3.7, p for trend = 0.01).

Women who receive estrogen replacement therapy may be more likely to undergo medical breast examination. This possible bias is discussed below.

Smoking

Most reports show no substantial effect of ever, former, or current smoking on either fibrocystic breast disease or fibroadenoma, even across different atypia grades (54, 56, 64, 65, 98–100); however, Berkowitz et al. (64, 95) found protective effects, and Nomura and Comstock (56) found deleterious effects.

Diet

Studies on the effect of diet are relatively recent, and therefore use more comparable definitions of benign breast disease. Results are contradictory, and no clear patterns have emerged.

Rohan et al. (101) reported that a higher daily intake of energy was associated positively with benign epithelial proliferative disease when cases were compared with biopsy controls (highest versus lowest quintile of total calories: RR = 1.6, 95 percent CI 0.9–3.0; p for trend = 0.04) and associated inversely when cases were compared with community controls (RR = 0.5, 95 percent CI 0.3–0.9; p for trend = 0.02). Lubin et al. (102) showed a positive association of higher intake of all foods with fibrocystic breast disease atypias of grade >3 using hospital and neighborhood controls.

Ingram et al. (103) found no association of total energy intake with epithelial hyperplasia, neither did Vobecky et al. (104), regardless of whether clinical or biopsied fibrocystic breast disease was examined.

A relative risk of about 0.5 was reported by Ingram et al. (103) for intake of various food items, such as sugar, eggs, chicken, and seafood, and by Hislop et al. (79) for frequent consumption of green vegetables. A similar conclusion was reached by Simard et al. (74) for patients who ate less meat, offal, and cooked vegetables.

Total fat intake has been variably associated with increased (101, 103, 104), decreased (101), or unchanged (103) risk of fibrocystic breast disease across studies. However, Lubin et al. (102), when combining both hospital and neighborhood controls, found a relative risk of 7.6 (95 percent CI 1.4–40.2) for severe atypias associated with food items containing more than 10 percent fat.

Baghurst et al. (105), using hospital controls, found a reduced risk of benign epithelial proliferative disease for the highest versus lowest quintile of fiber ingestion (RR = 0.5, 95 percent CI 0.2–0.8; p for trend = 0.02), especially in premenopausal women. A protective effect (RR = 0.6) was also present with community controls but was not statistically significant. In contrast, Rohan et al. (101), employing the same study population as Baghurst et al. (105) but using incident and prevalent cases instead of only incident cases, found no association between fiber and benign epithelial proliferative disease with hospital controls and a protective effect with community controls (p for trend across quintiles of fiber intake = 0.04). Another population-based case-control study (103) showed no association of fiber with epithelial hyperplasia or fibrocystic breast disease without hyperplasia, and a screening-based case-control study (104) found an increased risk of benign epithelial proliferative disease for women aged >50 years.

No consistent association between benign breast disease and use of vitamins has been observed (71, 79, 101, 103–105). Retinol and β -carotene were found to be protective by Rohan et al. (101) using community controls, but not with biopsy controls; this is contrary to findings in the studies by London et al. (71) and Ingram et al. (103). Vitamin E has long been used in the treatment of benign breast disease (106); although an intervention study of 26 patients reported a remission rate of 85 percent (107), later studies with a double-blind design conducted by the same group (108) and by Ernster et al. (109) failed to show a significant improvement of fibrocystic breast disease after treatment with vitamin E (compared with a placebo).

The effect of alcohol consumption on benign epithelial proliferative disease has been investigated in detail by Rohan et al. (76). There was no indication of an association using either biopsy controls ($RR = 1.0$) or population controls ($RR = 0.9$), even after stratification for degree of atypia.

Methylxanthine consumption

After a decade of intense investigation into a possible deleterious effect of methylxanthines (caffeine, theobromine, and theophylline) on fibrocystic breast disease, there is no strong support for an association. Reports on uncontrolled and nonrandomized case series published in 1979 and 1981 (9–11) showed that caffeine restriction dramatically improved benign breast disease symptomatology. The etiologic hypothesis was that methylxanthines present in coffee inhibited cyclic adenosine monophosphate (AMP) and guanylic acid (GMP) phosphodiesterases, and activated a protein kinase. This resulted in an overproduction of fibrous tissue and cystic fluid, leading to benign breast disease. These first results were supported by some case-control studies (66, 67) but not all (37, 110). The strongest counter-evidence, however, came from studies that measured the amount of exposure in milligrams of methylxanthines (68, 111, 112); these studies found no consistent association with fibrocystic breast disease across populations or across control groups (112). Methylxanthine consumption has not been found to be related to fibroadenoma (66–68).

POTENTIAL BIASES

Epidemiologic studies of benign breast disease require special attention to guard against the occurrence of selection (including detection and surveillance) bias, misclassification, and incidence/prevalence biases.

Selection

In the "Methods" section, we estimated that only 10–20 percent of benign breast disease cases are histologically diagnosed. Study validity will therefore be compromised if the selection process differs across compared groups (case-control or exposed-nonexposed) because of differential access to medical care (selection bias), the diagnostic process (detection bias), or intensity of medical care (surveillance bias).

The observed association between high socioeconomic status and benign breast disease may be due to selection bias. Women with more education or higher socioeconomic status may more likely consult a physician for benign disorders, or examine their breasts more frequently, than women from lower social

groups. This association between education or income variables and risk of benign breast disease may persist even when cases are restricted to histologically confirmed benign breast disease since similar differential selection process according to social factors may occur for access to biopsy.

The possibility of detection bias has been raised as a possible explanation for the inverse relation of obesity to benign breast disease; nodules may be easier to detect in thin women (with less fat in their breasts) than in obese women. It is of note that the anthropometric basis of this detection bias is still elusive, since it has not been established that obese women have larger breasts than nonobese women. Sasano et al. (39), in an autopsy series, found that body mass index was positively correlated with total mammary volume (fat and gland) but not with glandular volume. Hislop et al. (52) showed that body mass index and breast size were independently associated with benign breast disease, breast size being the major factor before age 30 years and obesity after age 30 years.

The mechanism leading to uncompensated surveillance bias is not straightforward; i.e., increased medical surveillance of women taking estrogen replacement therapy may explain (totally or in part) why prolonged exposure to this therapy increases the risk of fibrocystic breast disease. On the other hand, the inverse trend between duration of oral contraceptive use and risk of fibrocystic breast disease could also be due to surveillance bias if physicians withhold oral contraceptives from women with benign breast disease. Indeed, it was shown in 1977 (4) that one third of physicians thought that benign breast disease was a contraindication to prescribing oral contraceptives, and that many women with benign breast disease stopped using oral contraceptives following medical advice.

Although the potential for selection bias is large, for the reasons just described, the conclusions presented here were strongly influenced by the results of studies that seriously attempted to prevent selection bias by comparing groups that had undergone a similar selection process. In an Australian case-control study (54, 76, 98, 101, 105, 112), for example, population controls were matched to cases by socioeconomic grading of area of residence. It was reassuring to note on grounds of comparability that breast self-examination was practiced with equal frequency in cases and in both types of controls (a matched population control group and an unmatched biopsy control group) (54).

Similarly, detection bias can be prevented if the likelihood of detection of the lesion is similar across the compared groups. In that Australian study (54, 76, 98, 101, 105, 112), two control groups were chosen,

one of which comprised women who had undergone breast biopsy in the same way as had the cases but whose breasts were histologically normal. It was, therefore, important to find that the inverse association between obesity and risk of fibroadenoma persisted when cases were compared with biopsied controls, since detection of the lesion might also be affected by body mass in biopsied controls (54).

Misclassification

As in studies of breast cancer, etiologic studies of benign breast disease can be plagued by misclassification of exposure and by recall bias (for example, if a woman feels an improvement or a worsening of her clinical symptoms while using oral contraceptives, she may recall the use of the oral contraceptives differently than would a woman without benign breast disease). In addition, because benign breast disease is such a loosely defined pathology (as discussed previously), misclassification of disease is also a serious concern.

Several scenarios of disease misclassification are plausible. Controls may suffer from undetected benign breast disease, or clinically diagnosed patients may be classified as having benign breast disease but in reality have normal breasts. The proportion of clinically suspected benign breast disease that corresponds to physiologic changes is unknown, but it could be as high as 50 percent, and this is because incidence rates of unbiopsied benign breast disease are about twice as high as those of biopsied benign breast disease; in the study of oral contraceptive users by Brinton et al. (51), incidence rates per 100,000 woman-years were 187 for fibrocystic breast disease biopsies and 293 for clinical nodules without biopsy, and in the study by Hislop et al. (52), rates were 540 for biopsied disease (any diagnosis) and 1,040 for nonbiopsied symptomatic mastopathies.

A more subtle form of misclassification may occur when the tissue obtained by biopsy is not representative of the pathology of the entire breast. Lesions in the breast tissue surrounding the biopsy area may have a different degree of atypia than the biopsied tissue. Biopsy can also detect fibroadenoma lesions but not adjacent fibrocystic breast disease lesions; this results in misclassification of fibroadenoma as fibrocystic breast disease, or vice versa.

Misclassification of disease can also result from diagnostic inaccuracy. In a case-control study conducted in Connecticut by Berkowitz et al. (85), it was estimated that the agreement between two pathologists reading the same biopsy slides of fibrocystic breast disease and fibroadenoma was fair ($\kappa = 0.64$) and

slightly lower than the intraobserver reliability ($\kappa = 0.79$).

Using only histologically confirmed cases can limit the extent of misclassification of disease in cases. However, this gain in validity may be counterbalanced by increased selection, since access to successful biopsy may differ according to socioeconomic status, obesity, etc.

In this review special attention has been given to studies that attempted to reduce the likelihood of disease misclassification. For example, in a New Haven, Connecticut, study (53, 64, 66, 85, 86, 94), all biopsy slides of women with a presumptive diagnosis of fibrocystic breast disease were reevaluated by a pathologist, and a representative sample was then reviewed by a second pathologist. Of 981 potential cases, 634 (65 percent) were retained as fibrocystic breast disease. Similarly, in a Boston, Massachusetts, nested case-control study, the slides of 272 women with suspected incident fibrocystic breast disease were identified for review, of which 34 (12.5 percent) had to be excluded (72).

Temporality

Because benign breast disease is nonfatal and is likely to remain undetected for many years, it is not always possible to decide whether or not the lesion preceded exposure to a possible risk factor. This phenomenon may occur even in studies that exclude women with a previous history of benign breast disease. The main advantage of cohort studies over case-control studies when studying benign breast disease etiology is that chances of including only those lesions occurring after exposure are improved.

SYNTHESIS

In the conclusion of her review, Ernster (1) called for a separation of fibroadenoma and fibrocystic breast disease and for implementation of the new classification for fibrocystic breast disease related to the subsequent risk of breast cancer. Recent studies have followed this advice, and their results have been reviewed here. They can be synthesized as follows.

Fibrocystic breast disease, but not fibroadenoma, is related to a woman's reproductive history. Nulliparity and late menopause may increase the risk of fibrocystic breast disease, while high parity may decrease the risk. On the other hand, age at menarche, age at first live birth, and breastfeeding are not consistently associated with fibrocystic breast disease.

These results suggest that the probability of aberrations of normal development and involution is increased by a higher cellular proliferation of the breast

epithelium (as, for example, during the second part of the ovulatory cycle) and is decreased by factors which slow the proliferation of breast cells (such as the glandular differentiation occurring after a full-term pregnancy). Thus, parity would protect against fibrocystic disease because parity influences full development of the breast; late age at menopause would be deleterious because of longer exposure to ovarian hormones. The absence of an effect of age at menarche and age at first live birth could be attributed to the age distribution of women with the disease, that is, early reproductive events may be too far removed in time from the perimenopausal years, during which the incidence of fibrocystic breast disease reaches its peak.

While endocrine etiology for benign breast disease has long been suspected, as symptomatology fluctuates with the menstrual cycle, it has not been demonstrated. In their review of the endocrine based studies of benign breast disease, Wang and Fentiman (113) could not identify a clear or consistent pattern of hormonal abnormalities, but this may have been due to the heterogeneity of conditions defined as benign breast disease. Sitruk-Ware et al. (114, 115) found that women with benign breast disease had a lower progesterone:estradiol ratio, and this was attributed to inadequate corpus luteum function. The identification of a hormonal origin of benign breast disease is further complicated by the fact that serum hormones may not reflect the local hormonal milieu of the breast: Ernster et al. (116) and Petrakis et al. (117) demonstrated that levels of estradiol and estrone were markedly (5–45 times) higher in breast fluid than in serum among both premenopausal and postmenopausal women, but these levels did not correlate with each other. Also, breast fluid estrogen levels do fluctuate (they are lower in parous premenopausal women than in nulliparous premenopausal women, and are positively correlated with time since last birth or since last breastfeeding), hampering the interpretation of hormonal differences between benign breast disease and normal breast fluids.

Obesity is protective against both fibroadenoma and fibrocystic breast disease. The protective effect of obesity is highly consistent across studies, even among those using biopsy controls. The biologic basis of this association may be related to the hormonal consequences of obesity—as, for example, the alterations of androgen metabolism involved in impaired ovulation (118).

The protective effect of oral contraceptives is suspected but has not been established. The protective effect of oral contraceptives may stem from a suppression of the peak in estrogen and progesterone levels that occurs during the second part of the menstrual cycle. This interpretation is debatable, however, since

Anderson et al. (119) found increased cell proliferation in breast tissue adjacent to benign lesions (mostly fibroadenomas) in nulliparous (but not parous) oral contraceptive users, which was related to the estrogen content of the oral contraceptives. In addition, Williams et al. (120) showed that oral contraceptive use was linked to a longer period of high proliferation of epithelial cells (and a decrease in estrogen receptor content) in normal breasts during the menstrual cycle. It is important to know whether the risk of benign breast disease differs according to the composition of oral contraceptives, but more data about the effects of different types of oral contraceptives are needed.

Estrogen replacement therapy may enhance benign breast disease risk. An increased risk of fibrocystic breast disease in estrogen replacement therapy recipients has been consistently found. As this observation is also compatible with increased medical attention among estrogen replacement therapy users, a surveillance bias remains an alternate explanation.

There are no known preventable risk factors for benign breast disease. Cigarette smoking, diet, and methylxanthines have not been found to be associated with benign breast disease in the current literature.

CONCLUSION

Endocrine factors are involved in the etiology of benign breast disease, but their precise roles remain to be elucidated. There are no known modifiable risk factors for benign breast disease. The only known protective factor, obesity, cannot be promoted because of its other potentially deleterious effects on a woman's health. The roles of oral contraceptives and estrogen replacement therapy need to be further investigated, with special attention paid to their pharmaceutical content. Despite the absence of associations in the general population, subgroup differences related to genetic susceptibility cannot be ruled out.

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